



Review

Wired for sound: The effect of sound on the epileptic brain

Melissa Jane Maguire

Consultant Neurologist & Honorary Clinical Associate Professor of Neurology, Department of Neurology, Leeds General Infirmary, Great George Street, Leeds LS1 3EX, UK

ARTICLE INFO

Keywords:

Epilepsy
Music
Mozart
Auditory
Ultrasound
Infrasound

ABSTRACT

Sound waves are all around us resonating at audible and inaudible frequencies. Our ability to hear is crucial in providing information and enabling interaction with our environment. The human brain generates neural oscillations or brainwaves through synchronised electrical impulses. In epilepsy these brainwaves can change and form rhythmic bursts of abnormal activity outwardly appearing as seizures.

When two waveforms meet, they can superimpose onto one another forming constructive, destructive or mixed interference. The effects of audible soundwaves on epileptic brainwaves has been largely explored with music. The Mozart *Sonata for Two Pianos in D major*, K. 448 has been examined in a number of studies where significant clinical and methodological heterogeneity exists. These studies report variable reductions in seizures and interictal epileptiform discharges. Treatment effects of Mozart *Piano Sonata in C Major*, K.545 and other composer interventions have been examined with some musical exposures, for example Hayden's *Symphony No. 94* appearing pro-epileptic. The underlying anti-epileptic mechanism of Mozart music is currently unknown, but interesting research is moving away from dopamine reward system theories to computational analysis of specific auditory parameters.

In the last decade several studies have examined inaudible low intensity focused ultrasound as a neuro-modulatory intervention in focal epilepsy. Whilst acute and chronic epilepsy rodent model studies have consistently demonstrated an anti-epileptic treatment effect this is yet to be reported within large scale human trials. Inaudible infrasound is of concern since at present there are no reported studies on the effects of exposure to infrasound on epilepsy. Understanding the impact of infrasound on epilepsy is critical in an era where sustainable energies are likely to increase exposure.

1. Introduction

Epilepsy is a common neurological condition affecting 50 million people worldwide. Epilepsy is defined by the International League Against Epilepsy (ILAE) as two or more unprovoked seizures more than 24 h apart or a single unprovoked seizure with a more than 60% risk of recurrence [1].

The causes of seizures are numerous, ranging from genetic aetiologies to those occurring as a consequence of a brain tumour, infection or stroke. Seizures manifest as a result of excessive synchronous electrical discharges within a network due to an imbalance in excitatory and inhibitory neurotransmitters. Seizures can have either a focal or generalised onset and observable clinical signs may vary depending on the cortical areas affected [2].

For around seven in ten people with epilepsy, seizures are controlled with anti-epileptic medication aimed at re-balancing neurotransmitters and electrical excitation. For the remaining three in ten, seizures are

intractable to medication and other treatment modalities such as epilepsy surgery or neuromodulation may be considered. People with intractable epilepsy are three times more likely to suffer depression, commit suicide and die a premature death due to sudden unexpected death in epilepsy (SUDEP) [3,4]. Uncontrolled seizures are also associated with a poorer quality of life (QOL) [5]. A very small proportion, around 3% of people with epilepsy are photosensitive requiring measures to reduce environmental exposures to flashing lights at certain frequencies [6].

Brain waves are oscillating electrical voltages in the brain measuring just a few millionths of a volt. Brainwaves can be measured using electroencephalography (EEG) a test widely used in clinical practice. Normal brain wave frequencies measured in Hertz (Hz) (cycles per second) range between 0.5Hz (delta waves) to >35Hz (gamma waves). During an epileptic seizure, brainwave morphologies change to take on fast spike-wave or sharp wave forms in rhythmic bursts of activity followed by slowing of brain waves [7].

E-mail address: melissamaguire@nhs.net.

<https://doi.org/10.1016/j.seizure.2022.09.016>

Received 8 June 2022; Received in revised form 8 September 2022; Accepted 23 September 2022

Available online 24 September 2022

1059-1311/© 2022 British Epilepsy Association. Published by Elsevier Ltd. This article is made available under the Elsevier license (<http://www.elsevier.com/open-access/userlicense/1.0/>).

There is an increasing body of evidence that sound waves in the form of audible tones or music may affect people with epilepsy [8]. Some patients may experience seizures whilst listening to music while others may notice a benefit from listening to music on their seizures [9]. The prevalence of music as a seizure trigger (musicogenic epilepsy) is unknown as it is not routine practice to test seizure provocation with sound waves during EEG. Sound waves however are not limited to frequencies audible to the human ear. There is a frequency spectrum of sound waves ranging from; infrasound (<20Hz), human audible range (20-20,000 Hz) to ultrasound (>20,000Hz) [10].

Since we are environmentally exposed to sounds of varying frequencies all the time, it is imperative to understand the impact of sound across the frequency spectrum on epilepsy. This by extension may assist in preventative seizure strategies, and could highlight potential neuro-modulatory treatments for seizures.

This review aims to summarise our understanding of the effect of sound across the spectrum on epilepsy. It discusses the nature of sound waves and how they could potentially interact with the epileptic brain to affect change in brain waves. The review will go on discuss studies observing pre-clinical and clinical effects of sound on epilepsy and studies investigating sound therapies in epilepsy.

References for this review were identified by searches of PubMed between 1969 and February, 2022, EMBASE and references from relevant articles. The search terms 'epilepsy' 'seizure' 'music' 'sound' 'infrasound' 'ultrasound' and 'Mozart' were used. There were no language restrictions. The final reference list was generated on the basis of relevance to the topics covered in this review.

2. The sound spectrum

Sound is defined as a vibration that propagates an acoustic wave through a medium such as gas, solid or liquid. As the source continues to vibrate the medium, the vibrations propagate away from the source at the speed of sound forming the sound wave. During propagation, waves can be reflected, refracted or attenuated by the medium. Sound is transmitted as longitudinal or compression waves (gas or liquid medium) or transverse waves (solid medium). Energy carried by oscillating sound waves transfers back and forth between the potential energy of extra compression (longitudinal waves) or displacement strain (transverse waves) and the kinetic energy of displacement velocity of particles within the medium. When sound is received (e.g. human ear), the sound is interpreted by its two elements of pressure and time. Four key components make up these two elements; frequency (inverse of wavelength),

amplitude (decibels), speed of sound (343metres/second) and direction. These components of sound are simplified diagrammatically as sinusoidal plane waves [11].

Humans are able to perceive sound at between 20 and 20,000Hz (17m- 17mm wavelength respectively). Although many species of animals (for example cats) can hear much wider ranges of frequencies [12]. Sounds resonating at frequencies <20Hz are termed 'infrasound' and >20,000Hz 'ultrasound' and these frequencies are usually outside the human audible range [13]. (Fig. 1)

Infrasound (<20Hz) can be generated artificially through explosions, sonic weapons, low speed fans, wind turbines, trains, building sway, subwoofers at music concerts and supersonic aircraft. Or, naturally from earthquakes, severe weather, lightning, and other sources. It is possible however for humans to detect infrasound if played at high volume under ideal pure sine wave conditions [14]. Audible sound (20-20,000Hz) is critical to our interactions with the outside world and is experienced in many ways through language and music [15]. When sounds combine that have high or low pitch, music is generated. Ultrasound (>20,000Hz) is similar in physical properties to audible sound and can be detected by bats and porpoises who use ultrasound for locating prey and obstacles. Ultrasound is used in many different fields including medical ultrasonography, industrial cleaning and chemical processing [16–18]. Beyond ultrasound is 'hypersound' (also termed praetersound or microsound) waves of frequencies greater than 10^{13} Hz. These very high frequency acoustic waves are being researched in the areas of nanoscale communication and quantum computing [19].

3. Sound and its interaction with the human brain

The human auditory apparatus detects sound waves via air and bone conduction. In air conduction, sound waves reach the outer ear and travel down the external acoustic meatus to reach the eardrum (tympanic membrane). Vibrating air particles cause the ear drum to vibrate. These vibrations are then amplified by the ossicles in the middle ear and transmitted from air to liquid within the cochlea (inner ear). Vibrations are analysed by the basilar membrane according to frequency and converted through stimulation of hair cells to electrical impulses. The auditory nerves relays these impulses via nuclei within the brainstem to the primary auditory cortex located in the superior temporal gyrus where electrical impulses (brainwaves) are perceived as sounds. In bone conduction, sound produces vibrations of the skull that are passed directly via compression of the otic capsule or indirectly through movement of the stapes footplate to the inner ear [20]. When music is

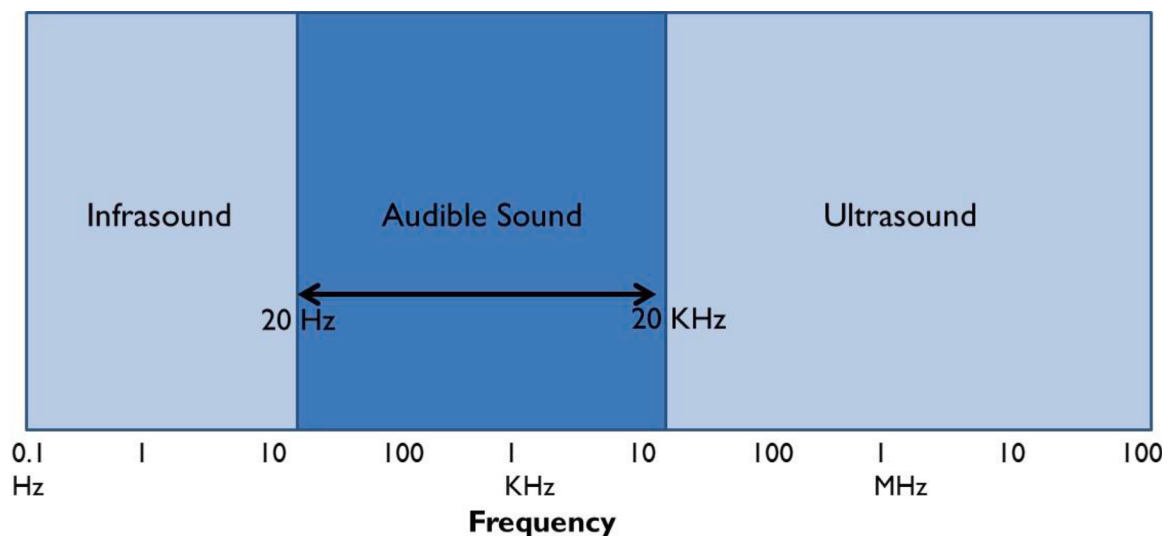


Fig. 1. The Sound Spectrum; frequency bands for acoustic waves.

perceived by the auditory system, it activates a complex network of neurons within auditory, mesolimbic, cerebellum and multisensory areas beyond the primary auditory cortex. Most functions of musical processing lateralise to the right brain hemisphere and include pitch processing, temporal processing, musical memory and emotional responses [21].

Within the brain cortex, brain waves are occurring which range in frequency depending on level of alertness or activity of humans. For example, delta waves (0.5Hz-4Hz) are associated with stage three and four slow wave dreamless sleep with activity declining in sleep through adult life [22]. Theta waves (4-8Hz) are linked to drowsy, meditative states and early phases of sleep and REM (Rapid Eye Moment) sleep [23, 24]. Hippocampal theta waves are also linked to navigation and memory formation [25,26]. Alpha waves (8-12 Hz) described by German Psychiatrist *Hans Berger* in 1924 are predominantly recorded from the occipital lobes during a relaxed state and with passive attention [27]. Growing evidence suggests that activity within this frequency band is important for spatial attention [28–30]. Beta waves (12-35Hz) are associated with active concentration, and increased sensory feedback during periods of static motor activity or where motor activity has to be voluntarily suppressed [31,32]. Gamma waves (>35Hz) are the fastest of brain waves, and have been shown to demonstrate feedforward connectivity across different brain regions in human and monkey neocortex [33]. In the epileptic state, high-frequency gamma oscillations at 60–150 Hz and fast ripples at 250– 500 Hz are seen at the initiation of epileptiform potentials and seizures [34]. There is evidence in the pre-ictal state of slow wave modulation of high frequency gamma via cross-frequency coupling which may have use in detecting the epileptogenic zone of patients [35–37].

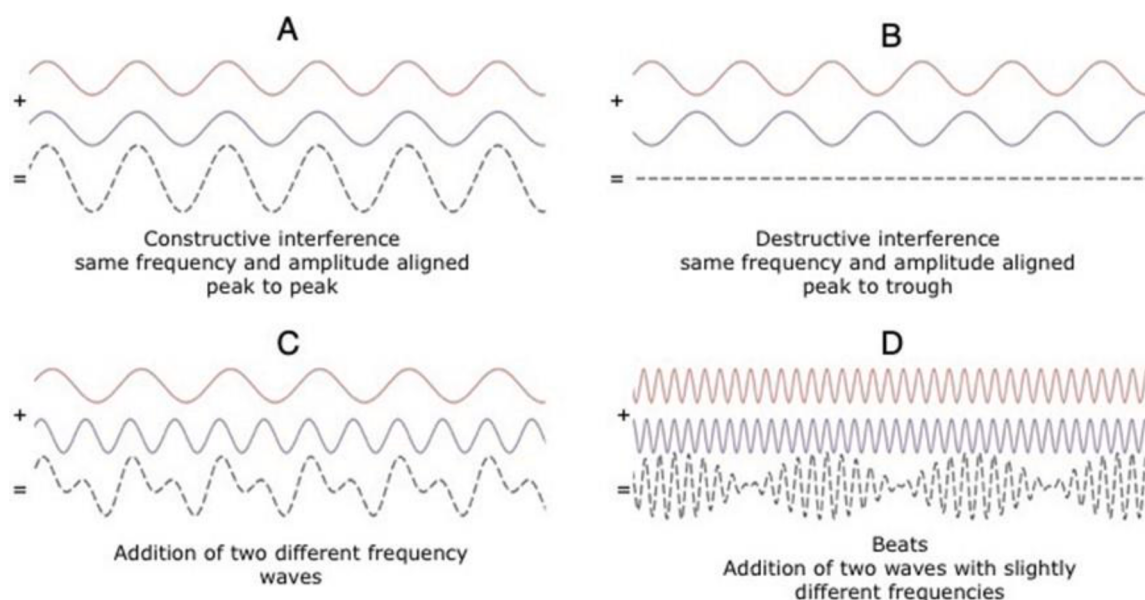
In physics, when two or more waves meet they superimpose themselves onto one another termed ‘superposition’. Superposition can be constructive or destructive. Constructive interference occurs when two waves add together in superposition creating waves with a cumulatively higher amplitude. In destructive interference, the two waves when added together cancel one another out. In order for waves to produce pure construction or destruction requires them to be precisely aligned. However, in most cases of wave superposition, a combination of

constructive and destructive interference is produced (Fig. 2) [38]. Superposition of two waves with non-identical frequencies produces a pulsing known as a beat. This is where waves are alternating between constructive and destructive interference which impacts on the amplitude of the resultant combined wave [39]. If two waves are similar in frequency, then this produces a wave of the average frequency but alternates in amplitude termed beat frequency. Musicians use this beat frequency to ensure two notes are in tune [40].

3.1. Brainwave entrainment and binaural beats

Audio brainwave entrainment has been studied through the application of binaural beats. This is where two sounds of slightly different frequencies are played at the same time, with the brain perceiving the difference in frequencies. For example, if a 300 Hz tone was played in one ear, and a 250 Hz tone was played in the other, the brain would perceive a 50 Hz tone. The importance of this is that soundwaves in our environment can induce certain brainwaves; thus, binaural beats could be used to produce specific, desired types of brain waves [39]. Binaural beats have been studied in the context of anxiety, acute pain and improving attention and focus of children during reading tasks. A review across studies have shown inconsistent results although a trend towards lower levels of anxiety are reported in many studies [41]. Inducing brain wave entrainment to slower frequencies was reported to reduce anxiety, whilst entrainment to alpha-beta ranges improved attention in children [42].

Binaural and monaural beats have also been investigated in the context of epilepsy using stereotactic EEG (depth electrode recordings) in ten patients. The researchers found that binaural and monaural beats modulate oscillations and phase synchronization. At lower frequencies <10Hz the brainwaves were noted to fall out of synchronisation and lose power at the frequency of the beat, whilst at 10-40Hz there was a notable increase in strength of brain waves at this frequency with entrainment [43]. A further study examined oscillations of brain waves in cortical regions remote from interictal epileptiform discharges (IEDs) using magnetic electroencephalography in 41 patients with focal epilepsy. Patients with frontal IEDs triggered inhibitory alpha-beta



© The University of Waikato Te Whare Wānanga o Waikato | www.sciencelearn.org.nz

Source: “Science Learning Hub – Pokapū Akoranga Pūtaiao, University of Waikato, www.sciencelearn.org.nz”

Fig. 2. Constructive and destructive interference of sound waves.

oscillations in remote posterior regions of the brain, with these oscillations correlating with a better cognitive profile. The study surmised that brain regions protect themselves from IEDs by generating inhibitory alpha-beta oscillations at distant cortical sites [44].

4. Clinical studies of sound and epilepsy

4.1. Infrasound

There have been numerous clinical studies examining the effects of infrasound on brain function. Many earlier uncontrolled clinical studies observed the effects of infrasound on industrial workers or populations within the vicinity of wind turbines, where symptoms of nausea, fatigue, ear pain, sleep disturbance and annoyance were reported [45–47]. Criticisms of these studies however relate to the fact that low frequency audible sounds were usually involved, thereby symptoms could not be exclusively attributed to infrasound [48]. There are three published reviews of observational studies examining health effects of wind turbine sound. These reviews conclude a robust association between the level of wind turbine sound and annoyance, but inconsistent results for sleep disturbance, cardiovascular and metabolic effects. There were no associations between wind turbine sound and mental health. There were no population studies examining the effects of wind turbine sound on epilepsy [49–51].

There have been several fMRI studies examining the effects of infrasound on brain activity. Exposure resulted in altered bold signal within the primary auditory cortex and superior temporal gyrus important for language in one study. Another study demonstrated that activity of the auditory cortex could be detected at 8Hz provided the volume was above the hearing threshold. Further studies observed recruitment of areas involved in stress response (amygdala) and attention (cingulate gyrus) suggesting wider brain activation beyond the auditory cortex. The same studies unexpectedly identified improvement in working memory tasks on exposure to 12 Hz infrasound [52–54].

A recently published randomised long-term exposure trial compared inaudible infrasound versus placebo over one month in 38 blinded healthy participants. It reported on mental health outcomes, somatic symptoms (e.g. sleep disturbance), and cognition/attention and brain structure using MRI scanning. An exclusion of this study were people with a central nervous system disorder (CNS) and/or those taking CNS medication excluding people with epilepsy. Infrasound had no effect on mental health outcomes, somatic symptoms or cognitive function. It did demonstrate perceptions of motor weakness and grey matter decline in brain areas that are associated with somato-motor- and cognitive functions such as working memory (bilateral cerebellum) and higher auditory processing (angular gyrus), comprising functions such as speech intelligibility/production or semantic/lexical processing and reading [55].

Several pre-clinical studies have previously identified alterations in neurochemical concentrations in rat brain models. Exposure to 8 or 16Hz at 120dB for two hours resulted in significant increases in glutamate concentrations while two other studies identified reductions in norepinephrine and dopamine concentrations [56–58]. These findings may be of significance in epilepsy.

In summary, wind turbine generated infrasound causes annoyance to exposed people with imaging evidence of an activated stress response. Short-term exposure also effects grey matter brain areas involved in somato-motor and cognitive function. Further studies inclusive of people with epilepsy and examining other parameters such as EEG are required to assess the impact of infrasound on epileptic brains.

4.2. Audible sound & music

4.2.1. Gamma auditory entrainment

The use of pure tone stimulation at 40Hz has been shown to improve condition states in Alzheimer's disease and stroke [59–62] where the

finding of reduced gamma oscillations are reported [63]. Quon et al. demonstrated that 40 Hz auditory stimulation could reduce IEDs in subjects with refractory epilepsy and high baseline IED rates [64]. However listening to a 40Hz tone for prolonged periods of time was not particularly pleasant for participants. Music has therefore been considered a more agreeable auditory stimulant and there is evidence that musical stimuli possessing more fundamental tones (higher gamma power) reduce numbers of IEDs [65]. The 40-Hz phenomenon is thought to relate to the activation of GABA interneurons, the primary regulators of excitatory and inhibitory neural activity. These interneurons are thought to synchronise cortical pyramidal neurons at gamma frequencies. Accordingly, regulation of these neurons may alleviate GABA dysregulation of epileptic networks [66–69].

4.2.2. Musical stimulation

In the last few decades researchers have examined the effects of music on epilepsy, from sonification of EEG data [70] in creating music to the observance of music therapy on IEDs [71].

Our understanding of musical processing comes from early brain injury work in the 19th century. Stewart et al. undertook an extensive review of studies observing structural brain defects and musical processing deficits from 38 case reports and 27 case series. The report summarised that most functions (pitch and temporal processing, musical memory and emotional responses) lateralised to the right hemisphere involving a network of areas beyond the primary auditory cortex [21]. Right hemispheric dominance for musical processing is observed at birth [72] and may reflect developmental specialisations of the right auditory cortex for better frequency resolution important for music when compared to the left auditory cortex which has better temporal resolution important for speech [73].

Music appears to impact on epileptic activity in a dichotomous way. From the coining of the term 'musicogenic epilepsy' by Critchley in 1937, there have been 126 cases of musicogenic epilepsy reported in the literature [74]. These are cases whereby a certain piece (melody of Marseillaise) type of music (jazz, choral, electronic, classical) instrument (piano, flute, organ) or composer (Beethoven, Wagner, The Beatles) appears to trigger seizures. Emotive and cognitive areas are reported to recruit early in the seizure as demonstrated by cases using fMRI imaging or invasive monitoring of musicogenic seizures using subdural electrodes [75–78]. These clinical studies provide evidence of an emotive component to musicogenic seizures as shown by activation of mesial temporal structures. Seizures stimulated by thinking or dreaming of music which ultimately recruits musical memory and emotion seem to support this theory [79–81]. It is possible that over time limbic connections are strengthened, thus promoting seizures on exposure [82]. Analysing cases of musicogenic epilepsy uncover a number of clinical features; female predominance, high musicality, right temporal lobe epilepsy and variable musical stimulus [75]. Since the musical trigger varied to a great extent, it is as yet unclear what or whether the acoustic parameters are relevant when considering the auditory exposure epileptogenic potential.

Music as a therapy in neurological disorders originated in the field of cognition. Rauscher et al. observed an immediate enhancement in spatial-temporal reasoning in college students exposed to 10 min of the Mozart Sonata K448 [83]. The authors subsequently coined the term the "Mozart effect." The same author also demonstrated improved maze navigation skills in rats and showed improved spatiotemporal abilities following exposed to the Mozart Sonata for Two Pianos in D Major, K.448 (K.448) when compared to control rats exposed to white noise or the music of Philip Glass [84].

Important to this review is the landmark work published in 1998 by Hughes et al. [85]. Interictal spike and wave complexes were shown to decrease in 23 out of 29 individuals with focal or generalised spike wave discharges when exposed to K.448. Several of these individuals had striking reductions in epileptiform activity during exposure including three participants in status epilepticus [85]. Further work by Hughes

et al. observed the longer term effects of K.448 in a child with Lennox Gastaut Syndrome and severe refractory drop seizures. The sonata was played every hour on the hour for ten minutes whilst awake. At the end of the awake period, the seizures had reduced from nine in the first four hours to one in the last four hours with a 44% reduction in epileptiform discharges [86]. Hughes et al. went on to explore the acoustic characteristics in order to explain the 'Mozart effect'. Computer analysis of 81 samples of Mozart music, 67 of JC Bach, 67 of JS Bach, 39 of Chopin and 148 from 55 other composers was performed converting musical notes into audio waves. Through computational analysis the study ascertained that long-term periodicity (10–60 s) was commonly found in Mozart music but absent from control music (old time pop piano tunes and music by Philip Glass) used in the previous exposure studies [87].

Furthermore, examining the melodic line of the music found significantly higher values of repeating notes in Mozart compared to Wagner, Bach, Beethoven and Chopin [87]. Further data by Hughes et al. was published on the acoustic properties of music by Hayden and Liszt. Mozart continued to score the highest on repetition of melody, although

Hayden was the second highest amongst the studied composers [88].

Since these early studies there has been further accumulating evidence of an anti-epileptic effect in epilepsy with K.448 as evidenced by a reduction in ictal and IEDs and seizure frequencies in humans and rodent epilepsy models. Lin et al. demonstrated a reduction in high-voltage rhythmic spike (HVRS) discharges in the Long Evans rat model of absence epilepsy [89] while Xing et al. demonstrated enhanced cognitive ability in pilocarpine status epilepticus rats [90].

Table 1 summarises published human clinical studies to date of K.448 and other music interventions in epilepsy.

There have been three published systematic reviews of K.448 and effectiveness in epilepsy [96–98].

Sesso et al. performed an updated systematic review and meta-analysis of 12 low-moderate quality studies involving 361 participants [96]. There were three randomised controlled trials (RCTs) of K.448 [91, 95, 99] and the remaining nine included studies were prospective randomised and non-randomised studies [65, 93, 94, 100–104]. The three RCTs; two parallel and one cross-over examined K.448 versus no

Table 1
Studies of music interventions in epilepsy

Author and Year	Study design	Sample size	AgeMean (range)years	Type of epilepsy	Intervention	Treatment Duration	Mean % reduction (IEDs)	Mean % reduction (seizures)
Turner 2004 [99]	RCT	2	(5–9)	BECTS	K.448 and Für Elise	18m/hr for 4h	K.448 39% (p<0.05) Für Elise (no change)	Not reported
Lin 2010 [65]	PS	58	8.2 (1–19.7)	F & G	K.448 and string K448	8m each	K.448 24% (p<0.05) String K448 (no change)	Not reported
Lin 2011a [100]	PS	11	9.1 (2.8–14.3)	F & G	K.448	8 m/day for 6 months	Not reported	K.448 53.6% (p = 0.017)
Lin 2011b [101]	PS	18	7.8 (0.6–14.3)	F & G	K.448	8 m/day for 6 months	K.448 72% (p < 0.001)	Not reported
Lin 2012 [102]	PS	39	7.3 (2.8–17.3)	F & G	K.448 and K.545	8 m(K448) then 9m (K.545)	K.448 33% (p<0.001) K.545 34%, (p < 0.001)	Not reported
Bodner 2012 [95]	RCT	36	36.9 (12–78)	F & G	K.448 and no stimulus	8m (each)/hr for 10h for 1year	Not reported	K.448 24%, (p = 0.024)
Lin 2013 [103]	PS	64	7.8 (2.9–15.3)	F & G	K.448 and K.545	8 m(K448) or 9m (K.545)	K.448 33%, (p < 0.001) K545 39%, (p < 0.001)	Not reported
Lin 2014 [91]	RCT	46	9.5 (0–18)	F & G	K.448 and no stimulus	8m/day for 6 months	K.448 82%, (p < 0.001)	Not reported
D'Alessandro 2017 [104]	PS	12	21.6 (5–39)	G	K.448	8m/day for 6 months	Not reported	K.448 20.5%, (p > 0.05)
Coppola 2018a [94]	PS	9	13.1 (1–24)	F & G	K.448 and Mozart music set	1 stimulus for 2hr/day for 15days	Not reported	K.448 37%, (p < 0.05)
Coppola 2018b [94]	PS	11	11.9 (1.5–21)	F & G	Mozart music set	1 stimulus for 2hr/day for 15days	Not reported	Mozart set 77%, (p < 0.05)
Grylls 2018 [93]	PS	45	7.8 (2–18)	-	K.448 and control music	2 stimuli (5m each) for 25 min	K.448 12% (p < 0.0005)	Not reported
Rafiee 2020 [92]	RCT	13	45.8(26–75)	F&G	K.448 and scrambled K.448	6.5m (K.448 or scrambled K.448/day) for 3mnths each	Not reported	K.448 35%
Štillová 2020 [107]	PS	18	(19–55)	F	K.448 and Hayden94	1 stimulus of K.448 then hayden94 over 2days	K448 32% (median) (p=0.094) No94 45% (increase)	Not reported
Paprad 2021 [105]	RCT	32	(0–18)	F	K.448 and no stimulus	8m each	K.448 67% (p<0.001) No stimulus 42%	Not reported
Quon 2021 [106]	PS	16	(24–68)	F	K.448, Wagner, violet noise	15sec or 90sec of each	k.448 66.5% (p<0.05) Wagner (no change) Violet noise (no change)	Not reported

RCT, randomised controlled trial; PS, prospective study; BECTS, benign epilepsy with centro-temporal spikes; F, focal; G, generalised; m, minute; hr, hour; IED, interictal epileptiform discharges

stimulation in a two-arm design or alternating stimulation with Beethoven's *Fur Elise* in the cross-over RCT. Nine meta-analyses were reported, although three were associated with significant heterogeneity and uncertainty around effect estimates. The study ascertained a mean percentage reduction in seizures by 31% and a mean percentage reduction in IEDs by 79% during treatment with K.448. The review synthesised data on another Mozart *Piano Sonata in C Major, K.545 (K.545)* which demonstrated 35% and 37% reduction in IEDs during treatment and after treatment. Studies comparing K.448 and K.545 showed no significant difference in efficacy on reducing IEDs. The review did not use meta-regression techniques to explain the statistical heterogeneity, although there were very clear differences in clinical characteristics, study design, exposures (once a day to prolonged nightly exposure) and reliance on scalp EEG measurements of included studies. The reported outcomes are also based on studies that were significantly underpowered therefore study inferences need to be interpreted with caution. The outcomes broadly agree with previous reviews by Dastgheib et al. [97] and Brackney et al. [98].

Since the publication of the updated systematic review by Sesso et al., there have been two further RCTs [92],[105]. One RCT observed the effect of K.448 vs. no music on IEDs in 32 children with epilepsy. The RCT reported a 67% reduction in IEDs in the K.448 group ($n=12$) which was statistically significant [105]. The other RCT observed once daily listening for three months of K.448 versus scrambled K.448 (no rhythmic structure) in a cross-over design of 13 adult participants. The authors reported a significant reduction in seizure frequency with K.448 by an average of 35% when compared to the three month control period. This study differed to other studies by using a spectrally similar control piece instead of no music/sound control. The result was comparable to seizure reductions reported in the systematic review [92].

There have been two stereotactic EEG (SEEG) studies reporting effects of K.448 and controlled music in epilepsy [106,107].

Quon et al. reported on 16 patients being evaluated for intracranial surgery with SEEG. The study evaluated the original K.448 with Wagner's Lohengrin (*Prelude to Act I*), a filtered version of K.448, violet noise, preferred genre and classical genre musical pieces (gamma spectrum matched/unmatched to K.448). The study sample was divided into two groups; 15 s exposure group and 90 s exposure group. IEDs rates were compared pre- and post-exposure. The study reported an average reduction in IEDs in seizure and non-seizure onset zones by 66% with K.448 exposure. Significant reductions in IEDs were evident at 30 s or longer K.448 exposure, but the observed reductions were not sustained beyond the 90 s stimulus, suggesting that longer exposure periods are required for a neuro-modulatory effect. There were no significant changes in the frequency of IEDs for any of the control music including the filtered version of K.448 where frequency components had been altered. The study observed that IEDs were preferentially reduced within bilateral frontal cortices with emerging increases in frontal theta activity. The authors inferred that emotional networks regulated by the frontal cortex which are internally evoked (as opposed to subjective) are important in the anti-epileptic effect. A theoretical analysis by the researchers of K.448 versus Wagner's control piece showed K.448 to have structurally organised melodic themes with harmony versus no recognizable melodies for Wagner. This together with frequency distortions in the filtered K.448 may shed lights on the acoustic components relevant to positive internal emotional responses and anti-epileptic effect [106].

Stillova et al. reported on the effects of K.448 and of Haydn's *Symphony No. 94* (Hayden No94) on IEDs in 18 patients with drug resistant focal (16 temporal, two extra-temporal) epilepsy. Hayden was chosen as a comparator due to shared emotional effects and repetition of harmonies. Patient were implanted with SEEG and over two consecutive days, IEDs were recorded for 10 min prior to music (Mozart or Hayden), during musical exposure, a 10 min break followed by further musical exposure (Mozart or Hayden). The order of listening was randomised. Listening to K.448 led to a median reduction of IEDs by 32%, and listening to No94 caused a 45% increase in IEDs relative to the pre-music

resting state. Left neocortical temporal epilepsy appeared more responsive to K.448 than mesial temporal epilepsy. Men and women responded differently to Hayden No94, with women showing a reduction in IEDs and men showing an increase in IEDs. Acoustic features of K.448 associated with a reduction in IEDs across all patients included; harmonic spectrum, high frequency parts and gradual reductions in tempo. The researchers were surprised by the lack of efficacy with Hayden No94 due to its perceived structural similarities to K.448 and were unable to explain why Hayden No94 performed particularly badly in men. Since patients declared emotional indifference to the music the researchers surmised that emotional dichotomy in males and females was unlikely to explain the difference and that other mechanisms were operant rather than an emotionally driven dopamine reward system theory. Harmonic spectrum appeared relevant to the efficacy of K.448 and was reported to be a more dominant acoustic structural property of K.448 than in Hayden No94 [107].

Several theories have been put forward to explain the effects of music on the brain. In the early studies of K.448 by Hughes et al., the clinical and computational findings suggested that music with a highly organised and repetitive structure showed the greater anti-epileptic effect. This prompted the authors to speculate that Mozart was more likely to resonate with the highly organised columnar structure of the neocortex and normalise any suboptimal functioning [85]. This theory was based on Mountcastle's work reporting on the existence of highly organised radial columnar structures within the neocortex. In this work, cortical connectivity patterns also demonstrated a columnar nature [108]. The Mozart effect has since been mathematically modelled using the 'Trion model' based on this columnar arrangement [109].

Further interesting theory based on the Trion model has emerged. Rafiee et al. hypothesise that the neuro-modulatory effect of music relates to signal predictability (spectral exponent (β)) of the music rather than entrainment through phase-locking [110]. This idea relates to the fractal spectral power distribution of the natural world, music and brain activity [111–114]. Power decays as $1/f^\beta$, where f is the frequency of the signal and β represents the spectral exponent. [111,112,115] If a signal is unpredictable, the spectral exponent will be small ($\beta < 0.5$) whereas highly predictable smooth signals with long-range correlations will have a larger exponent ($\beta > 2$) [116]. Healthy brain is attuned to track the scale free $1/f$ rhythm of the sensory world [114]. However activity in seizures and IEDs are dominated by large amplitude oscillations of high predictability and synchronicity departing from the $1/f$ statistic of healthy brain [117]. Levitin et al. examined 558 compositions and measured the β exponent reporting Beethoven music had larger β values (1.05) than Mozart (< 0.5) reflecting higher predictability [112]. It has been proposed that Mozart music could resonate and entrain highly organised cortical columns at a lower exponent brain state moving it towards a healthier $1/f$ scaling and could make the brain activity more resilient to seizure state [118]. Rafiee et al. proposes that the impact of music on the brain scaling exponent relates to the temporal structure β of the musical piece. The author acknowledges that further studies comparing predictable and unpredictable rhythms (high and low β) on cortical dynamics and seizure impact is needed.

Other studies have examined the impact of music on dopamine signalling. Using positron emission tomography (PET) and fMRI techniques, studies show there is dopamine release from the dorsal and ventral striatum when patients listen to music [119,120]. These areas are important in brain reward pathways [121]. Activity in the caudate nucleus is associated with the emotional peak in a piece of music which occurs when there is a shift in pattern or tone of music, that is, where music is unpredictable explaining initial euphoria to a new piece of song which wanes over time [122]. Several epilepsies are linked to a lack of dopamine in the striatum which by extension may affect the striatum's inhibitory action on thalamo-cortical connections promoting excitation [123–125]. Music, in particular pieces with unpredictable pattern may flood the brain with dopamine enhancing activity within the striatum and by extension leading to an anti-epileptic effect on thalamo-cortical

connections [126]. In musicogenic epilepsy there may be a learnt response to the exposure, whereby pre-frontal areas are preferentially stimulated, thus inhibiting limbic dopamine responses and propagating seizure activity [127]. Other researchers challenge the dopamine reward system theory since K.448 has demonstrated anti-epileptic effects in patients rendered unconscious by status epilepticus whereby a top-down control through attention and emotion are absent [85].

Lower parasympathetic tone is reported in epilepsy [128]. The effects of K.448 on parasympathetic activity in epilepsy has been explored by examining heart rate variability (HRV) [129,105]. Lin et al. reported reductions in epileptiform discharges and significant increase in parasympathetic parameters in 64 Taiwanese children with epilepsy. Parasympathetic tone was found to increase more in patients with generalised seizures. Thalamic modulation was considered a possible mechanism by the authors by which K.448 exerts its anti-epileptic effect [129]. A more recent single-blinded placebo controlled RCT by Paprad et al reported in addition to a significant reduction in epileptiform discharges a non-significant increase in parasympathetic tone in a smaller sample of 32 children with epilepsy and developmental delay exposed to 8 min of K.448 versus quiet environment [105].

4.3. Ultrasound

The use of ultrasound as a neuro-modulatory treatment in epilepsy has gained interest in the last decade with several studies examining the effects of low intensity focused ultrasound (US) in epilepsy both in animal models and human participants.

In 2011, Min et al. used focused US in a pentylenetetrazol-induced acute epileptic rat model. The study reported suppression of EEG epileptic bursts activity with no evidence of damage to sonicated brain [130]. Further studies using chronic rodent models of epilepsy, the murine Kainic Acid (KA) chronic temporal lobe epilepsy model and the pentylenetetrazol rat epilepsy model have demonstrated similar suppression of EEG activity and seizures without tissue damage [131,132]. Another study using the KA-induced temporal lobe epilepsy murine model applied low intensity pulsed or continuous US (500 kHz) in the CA3 field of the hippocampus and recorded local field potentials. The study demonstrated suppression of burst epileptiform activity and slow frequency dynamics leading to a reduction in phase amplitude coupling. The study researchers surmised that by affecting fast and slow wave oscillations effectively caused destructive interference resulting in a reduction in synchronous discharges [133]. A recent study using low-frequency US targeted to the hippocampus in the KA-induced epilepsy rat model analysed the EEG functional brain network. The study reported a reduction in strength (measured by phase-locking value) and transmission capability (measured by cluster coefficient and path

length) of network connections at low (theta) frequency bands on exposure to US inhibiting synchronisation [134].

There are three case reports [135–137] and three small cohort studies [138–140] observing the effectiveness of low intensity transcranial focused US in adults with temporal lobe epilepsy (Table 2). Three of these studies [137], [139,140] reported on the neuro-modulatory effect in patients who were being evaluated for epilepsy surgery. The other three studies report cases of lesion ablation with low intensity US [135–136], [138].

Lee et al. examined low intensity US (0.75 MI, 30% duty cycle, 600 s) in six patients whose seizure onset zone had been identified by stereotactic SEEG. Application of focused US to the seizure onset zone occurred at day 10 of SEEG monitoring and clinical seizure activity and IEDs were monitored over a period of three days post sonication. Two thirds of participants experienced a reduction in IEDs within 72 h after treatment and one third an increase in IEDs. Clinical seizures were recorded in three of six patients post sonication, however the frequency was reduced in two patients and increased in one patient during this short follow-up period. One patient experienced uncomfortable scalp heating and the treatment needed to be halted. Spectral analysis of signals from electrode contacts in the target zone revealed decreased amplitudes in the delta to beta bands post sonication. This outcome was not observed in non-target zone electrodes. One patient had two sonication treatments with a greater reduction in waveform amplitude suggesting a possible dose-effect. MRI imaging did not demonstrate any evidence of US related damage [139].

Brinker et al. reported on a 26 year old female participant who received pulsed low intensity US in drug resistant temporal lobe epilepsy. The study reported on a laboratory-built device platform designed to investigate PLIFUS neuromodulation of the human hippocampus. The purpose was not to demonstrate effectiveness of US and therefore no clinical information regarding the exposure is reported [137].

Stern et al. reported on the safety of 650 kHz transcranial focused US neuromodulation in eight patients undergoing intracranial surgery for drug resistant temporal lobe epilepsy. The ultrasound was focused on the region within the temporal lobe to be resected. Functional MRI of the brain was obtained throughout the US session. The primary outcome was to determine histologic damage which was absent in seven of eight participants. The results were inconclusive for the remaining participant. Pre- and post-US neuropsychometric testing revealed a reduction in verbal memory, but since the study did not involve a control (sham) arm there was uncertainty around causation being US sonication [140].

Several mechanisms linking US treatment to anti-epileptic effect have been postulated. The most popular proposed mechanism is the mechanical bio-effects of low frequency US on lipid bilayer tension. This alteration in tension may affect the gating kinetics of ion channels

Table 2
Studies of ultrasound in epilepsy

Author and Year	Study design	Sample size	AgeMean (range)years	Type of epilepsy	Intervention	Treatment Duration	Treatment outcomes	Adverse effects
Parker 2019 [138]	PS	2	-	F	MRgFUS (Lesioning)	Not reported	Not reported	None
Abe 2020 [136]	CR	1	36	F	MRgFUS at 42–44°C (Lesioning)	Repetitive 10–20s	Seizure free	Dizziness
Brinker 2020 [137]	CR	1	26	F	PLIFUS (5–2.25 W/cm ² , duty cycle 36%–50%)	7s inter-stimulations lasting 140s	Not reported	None
Yamaguchi 2020 [135]	CR	1	26	F	MRgFUS at 50–53°C (Lesioning)	6 sonications at 5 sites	Seizure free	Nausea and vomiting
Stern 2021 [140]	PS	8	(22–65)	F	TFUS (650KHz)	8 sonications	Not reported	Reduction in verbal memory No histopathologic damage
Lee 2022 [139]	PS	6	31.5 (26–42)	F	LIFUP (2.8 W/cm ² , 75 MI, 30% duty cycle, 600 s)	1 sonication- 10min	33% reduction in seizures	Heat and FND

CR, case report; PS, prospective study; F, focal; MRgFUS, magnetic resonance-guided focused ultrasound; PLIFUS, pulsed low-intensity focused ultrasound; TFUS, transcranial focused ultrasound; LIFUP, low-intensity focused ultrasound pulsation; s, second; mins, minutes; FND, functional neurological disorder

(voltage-gated Na⁺ and Ca²⁺) and synaptic receptors important in regulating neuronal activity [141]. This by extension may alter network activity reducing propagation of epileptic discharges within epileptogenic zones [142]. Another putative mechanism is the impact of mechanical stress on adenosine signalling. Evidence for this mechanism comes from a study of deep brain stimulation in essential tremor where adenosine augmentation led to a reduction in tremor [143]. Other authors propose that US interferes with neuronal activity through the PI3K-Akt-mTOR pathway as evidenced by a reduction in epileptic spikes in the PTZ-epilepsy rodent model [132]. A further study has demonstrated a neuroprotective effect of US in the KA hippocampal epileptic mouse model. This study observed a prolonged latency of seizures and improved anxiety behaviours in mice stimulated with low intensity US versus sham stimulation. Apoptosis was also reduced with US as evidenced by downregulation of BAX and c-caspase 3 proteins together with reductions in proteins related to inflammation through altered JNK pathway activity [144].

In summary the use of low intensity US in epilepsy requires further study in larger populations of patients, using different parameters with longer durations of follow-up. Nevertheless, current evidence suggests that low intensity US may have anti-epileptic effects. The short acoustic wavelength of US enables focused sonication to regions limited to several millimetres with no evidence of tissue damage. The mechanisms by which US modulates epileptogenic activity remain unclear, but mechanical bio-effects through altered kinetics of voltage gated ion channels and destructive wave interference may impact on synchronous activity in epilepsy.

5. Summary & conclusions

The impact of the sound spectrum and sound neuromodulation in epilepsy remains an interesting yet under-represented area of research. Current evidence reports the potential of sound to affect changes on epileptiform discharges in both positive and negative ways. Most research has focused on the *Mozart K.448 Sonata* with heterogeneous and low certainty evidence demonstrating an average reduction in seizures by one third and an 80% reduction in IEDs. Evidence emerging within the last decade report promising pre-clinical results with focused low intensity ultrasound in focal epilepsies. At present published data in human subjects is very small and efficacy and adverse event outcomes are yet to be reported from larger scale human trials. Furthermore, focussed ultrasound may pose a practical challenge to implementation in healthcare systems since it requires access to a trained therapist with associated cost implications. Compare this to a proven efficacy music intervention which could be administered at home with no cost burden or concerns over significant adversity.

There is a clear knowledge gap on the effect of infrasound in people with epilepsy. The lack of exposure or therapeutic studies in broad populations is acknowledged in public health reports [13]. Given public health concerns and the likely increase in sustainable energies including wind farms together with climate change [145], consideration should be taken into furthering research through preclinical exploration of infrasound in epilepsy animal models.

The exact mechanism underpinning the effect of sound or music on epileptic brain is currently unknown. Basic parameters of the sound spectrum, for example pure tone frequencies have not been adequately explored in epilepsy although their practical utility as a therapy for epilepsy is questionable. For example do frequencies closer to the frequency of seizures have greater ability to entrain the brain to an anti-epileptic state? Do lower frequencies within the infrasound range have a negative impact on epileptic brains? Does it matter whether the frequencies are delivered within a known epileptic zone or at remote sites?

Computational analysis may offer the opportunity to explore ranges of acoustic parameters pertinent to the anti-epileptogenic effect of music. Some interesting computational findings have uncovered that music with less predictable structures are more anti-epileptic. This

might make sense, since human brains are wired for neural pattern recognition and conditioning. So when music is unpredictable it may alert protective brain networks to generate higher brain frequencies that could exert seizure inhibition through GABA interneurons. Understanding biomechanical effects further may enable the development of musical neuro-modulations for epilepsy including status epilepticus.

Declaration of Competing Interest

I have no conflict of interest to disclose. I confirm that I have read the Journal's position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

Acknowledgments

None

References

- [1] Fisher RS, Acevedo C, Arzimanoglou A, Bogacz A, Cross JH, Elger CE, et al. ILAE official report: a practical clinical definition of epilepsy. *Epilepsia* 2014;55(4):475–82.
- [2] Fisher RS, Cross JH, French JA, Higurashi N, Hirsch E, Jansen FE, et al. Operational classification of seizure types by the International League Against Epilepsy: Position Paper of the ILAE Commission for Classification and Terminology. *Epilepsia* 2017;58(4):522–30.
- [3] Fiest KM, Dykeman J, Patten SB, Wiebe S, Kaplan GG, Maxwell CJ, et al. Depression in epilepsy: a systematic review and meta-analysis. *Neurology* 2013;80(6):590–9.
- [4] Sveinsson O, Andersson T, Mattsson P, Carlsson S, Tomson T. Clinical risk factors in SUDEP: A nationwide population-based case-control study. *Neurology* 2020;94(4):e419–29.
- [5] Taylor RS, Sander JW, Taylor RJ, Baker GA. Predictors of health-related quality of life and costs in adults with epilepsy: a systematic review. *Epilepsia* 2011;52(12):2168–80.
- [6] Martins da Silva A, Leal B. Photosensitivity and epilepsy: Current concepts and perspectives-a narrative review. *Seizure* 2017;50:209–18.
- [7] Binnie CD. Epilepsy in adults: diagnostic EEG investigation. In: Kimura J, Shibasaki H, editors. Recent advances in clinical neurophysiology. Amsterdam: Elsevier; 1996. p. 217–22.
- [8] Maguire M. Music and its association with epileptic disorders. *Prog Brain Res* 2015;217:107–27.
- [9] Maguire M. Epilepsy and music: practical notes. *Pract Neurol* 2017;17(2):86–95.
- [10] Gelfand SA. Essentials of audiology. 3rd Ed. USA: Thime; 2009.
- [11] Hazewinkel M. *Encyclopaedia of mathematics* (set). Kluwer; 1994.
- [12] Heffner RS. Primate hearing from a mammalian perspective. *Anat Rec A Discov Mol Cell Evol Biol* 2004;281(1):1111–22.
- [13] Hanson MA. *Health effects of exposure to ultrasound and infrasound: report of the independent advisory group on non-ionising radiation*. Chilton, GB. Health Protect Agency 2010:180.
- [14] Watanabe T, Möller H. Low frequency hearing thresholds in pressure field and in free field. *J Low Freq Noise Vibr Act Control* 1990;9(3):106–15.
- [15] Purves D, Augustine GJ, Fitzpatrick D, Katz LC, Lamantia AS, McNamara J, et al. *Neuroscience*. editors. 2nd edition. Sunderland (MA): Sinauer Associates; 2001. The Audible Spectrum.
- [16] Escoffre J, Ayache B. *Therapeutic Ultrasound*. Ed. Jean-Michel Escoffre and Ayache Bouakaz. Cham: Springer, 2016. Print.
- [17] Mason TJ. Developments in ultrasound–non-medical. *Prog Biophys Mol Biol* 2007;93(1–3):166–75.
- [18] Leighton TG. What is ultrasound? *Prog Biophys Mol Biol* 2007;93(1–3):3–83.
- [19] Clerk AA, Lehnert KW, Bertet P, Petta JR, Nakamura Y. Hybrid quantum systems with circuit quantum electrodynamics. *Nat. Phys.* 2020;16:257–67.
- [20] Yost William A. *Fundamentals of Hearing: An Introduction*. San Diego: Academic Press; 2007. Print.
- [21] Stewart L, von Kriegstein K, Warren JD, Griffiths TD. Music and the brain: disorders of musical listening. *Brain* 2006;129(Pt 10):2533–53.
- [22] Colrain IM, Crowley KE, Nicholas CL, Afifi L, Baker FC, Padilla M, et al. Sleep evoked delta frequency responses show a linear decline in amplitude across the adult lifespan. *Neurobiol Aging* 2010;31(5):874–83.
- [23] Aftanas LI, Golosheikine SA. Human anterior and frontal midline theta and lower alpha reflect emotionally positive state and internalized attention: high-resolution EEG investigation of meditation. *Neurosci Lett* 2001;310(1):57–60.
- [24] Barker W, Burgwin S. Brain wave patterns accompanying changes in sleep and wakefulness during hypnosis. *Psychosom Med* 1948;10(6):317–26.
- [25] Lega BC, Jacobs J, Kahana M. Human hippocampal theta oscillations and the formation of episodic memories. *Hippocampus* 2012;22(4):748–61.
- [26] Ekstrom AD, Caplan JB, Ho E, Shattuck K, Fried I, Kahana MJ. Human hippocampal theta activity during virtual navigation. *Hippocampus* 2005;15(7):881–9.

- [27] Berger H. Über das Elektrenkephalogramm des Menschen. *Archiv für Psychiatrie und Nervenkrankheiten* 2005;87:527–70.
- [28] Jensen O, Mazaheri A. Shaping functional architecture by oscillatory alpha activity: gating by inhibition. *Front Hum Neurosci* 2010;4:186.
- [29] Foxe JJ, Snyder AC. The role of alpha-band brain oscillations as a sensory suppression mechanism during selective attention. *Front Psychol* 2011;5(2):154.
- [30] Foster JJ, Sutterer DW, Serences JT, Vogel EK, Awh E. Alpha-band oscillations enable spatially and temporally resolved tracking of covert spatial attention. *Psychol Sci* 2017;28(7):929–41.
- [31] Baker SN. Oscillatory interactions between sensorimotor cortex and the periphery. *Curr Opin Neurobiol* 2007;17(6):649–55.
- [32] Baumeister J, Barthel T, Geiss KR, Weiss M. Influence of phosphatidylserine on cognitive performance and cortical activity after induced stress. *Nutr Neurosci* 2008;11(3):103–10.
- [33] Van Kerkhove T, Self MW, Dagnino B, Gariel-Mathis MA, Poort J, van der Togt C, Roelfsema PR. Alpha and gamma oscillations characterize feedback and feedforward processing in monkey visual cortex. *Proc Natl Acad Sci U S A* 2014; 111(40):14332–41.
- [34] Worrell G, Gotman J. High-frequency oscillations and other electrophysiological biomarkers of epilepsy: clinical studies. *Biomark Med* 2011;5(5):557–66.
- [35] Alvarado-Rojas C, Valderrama M, Fouad-Ahmed A, Feldwisch-Drentrup H, Ihle M, Teixeira CA, et al. Slow modulations of high-frequency activity (40–140-Hz) discriminate preictal changes in human focal epilepsy. *Sci Rep* 2014;4:4545.
- [36] Jacobs J, Wu JY, Perucca P, Zelmner R, Mader M, Dubeau F, et al. Removing high-frequency oscillations: a prospective multicenter study on seizure outcome. *Neurology* 2018;91(11):e1040–52.
- [37] Guirgis M, Chinvarun Y, Del Campo M, Carlen PL, Bardakjian BL. Defining regions of interest using cross-frequency coupling in extratemporal lobe epilepsy patients. *J Neural Eng* 2015;12(2):026011.
- [38] Radi H, Rasmussen J. Superposition of sound waves In: *Principles of Physics*. Undergraduate lecture notes in physics. Berlin, Heidelberg: Springer; 2013. p. 531–60.
- [39] Oster G. Auditory beats in the brain. *Sci Am* 1973;229(4):94–102.
- [40] Campbell M, Greated C, Myers A. Musical instruments: history, technology and performance of instruments of western music. 1st ed. Oxford: Oxford University Press; 2004. p. 26.
- [41] Chaieb L, Wilpert EC, Reber TP, Fell J. Auditory beat stimulation and its effects on cognition and mood states. *Front Psychiatry* 2015;6:70.
- [42] Kennel S, Taylor AG, Lyon D, Bourguignon C. Pilot feasibility study of binaural auditory beats for reducing symptoms of inattention in children and adolescents with attention-deficit/hyperactivity disorder. *J Pediatr Nurs* 2010;25(1):3–11.
- [43] Becher AK, Höhne M, Axmacher N, Chaieb L, Elger CE, Fell J. Intracranial electroencephalography power and phase synchronization changes during monaural and binaural beat stimulation. *Eur J Neurosci* 2015;41(2):254–63.
- [44] Pellegrino G, Hedrich T, Sziklas V, Lina JM, Grova C, Kobayashi E. How cerebral cortex protects itself from interictal spikes: The alpha/beta inhibition mechanism. *Hum Brain Mapp* 2021;42(11):3352–65.
- [45] Bolin K, Bluhm G, Eriksson G, Nilsson ME. Infrasound and low frequency noise from wind turbines: exposure and health effects. *Environ Res Lett* 2011;6(3): 035103.
- [46] Persinger MA. Infrasound, human health, and adaptation: An integrative overview of recondite hazards in a complex environment. *Nat Hazard* 2014;70(1): 501–25.
- [47] Leventhall G. What is infrasound? *Prog Biophys Mol Biol* 2007;93(1–3):130–7.
- [48] Leventhall G, Pelmear P, Benton S. A review of published research on low frequency noise and its effects. Department for Environment, Food and Rural Affairs; 2003.
- [49] Van Kamp I, van den Berg F. Health effects related to wind turbine sound: an update. *Int J Environ Res Public Health* 2021;18(17):9133.
- [50] Van Kamp I, Simon S, Notley H, Baliatsas C, van Kempen E. Evidence relating to environmental noise exposure and annoyance, sleep disturbance, cardio-vascular and metabolic health outcomes in the context of IGCN (N): a scoping review of new evidence. *Int J Environ Res Public Health* 2020;17(9):3016.
- [51] Baliatsas C, van Kamp I, van Poll R, Yzermans J. Health effects from low-frequency noise and infrasound in the general population: Is it time to listen? A systematic review of observational studies. *Sci Total Environ* 2016;557:558: 163–9.
- [52] Dommes E, Bauknecht HC, Scholz G, Rothemund Y, Hensel J, Klingebiel R. Auditory cortex stimulation by low-frequency tones-an fMRI study. *Brain Res* 2009;1304:129–37.
- [53] Weichenberger M, Bauer M, Köhler R, Hensel J, Forlim CG, Ihlenfeld A, Ittermann B, Gallinat J, Koch C, Kühn S. Altered cortical and subcortical connectivity due to infrasound administered near the hearing threshold - evidence from fMRI. *PLoS One* 2017;12(4):e0174420.
- [54] Weichenberger M, Köhler R, Bauer M, Hensel J, Brühl R, Ihlenfeld A, et al. Brief bursts of infrasound may improve cognitive function—an fMRI study. *Hear Res* 2015;328:87–93.
- [55] Ascone L, Kling C, Wiczorek J, Koch C, Kühn S. A longitudinal, randomized experimental pilot study to investigate the effects of airborne infrasound on human mental health, cognition, and brain structure. *Sci Rep* 2021;11(1):3190.
- [56] Guo-You F, Jing-Zao C, Ke-Yong J. Changes of glutamate in brain of rats exposed to infrasound. *J Fourth Mil Univ* 1999;20(4):288–90.
- [57] Spyrali C, Papadopoulou Z, Zis B, Varonos D. Effects of diazepam-infrasounds combination on locomotor activity and avoidance behaviour of rats. *Pharmacol Biochem Behav* 1980;12(5):767–71.
- [58] Spyrali C, Papadopoulou-Daifoti Z, Petounis A. Norepinephrine levels in rat brain after infrasound exposure. *Physiol Behav* 1978;21(3):447–8.
- [59] Adaikhan C, Middleton SJ, Marco A, Pao PC, Mathys H, Kim DN, et al. Gamma Entrainment Binds Higher-Order Brain Regions and Offers Neuroprotection. *Neuron* 2019;102(5):929–43. e8.35.
- [60] Iaccarino HF, Singer AC, Martorell AJ, Rudenko A, Gao F, Gillingham TZ, et al. Gamma frequency entrainment attenuates amyloid load and modifies microglia. *Nature* 2016;540(7632):230–5.
- [61] Martorell AJ, Paulson AL, Suk HJ, Abdurrob F, Drummond GT, Guan W, et al. Multi-sensory Gamma Stimulation Ameliorates Alzheimer's-Associated Pathology and Improves Cognition. *Cell* 2019;177(2):256–71. e22.
- [62] Zheng W, Minama Reddy GK, Dai F, Chandramani A, Brang D, Hunter S, et al. Chasing language through the brain: successive parallel networks. *Clin Neurophysiol* 2021;132(1):80–93.
- [63] Ribary U, Ioannides AA, Singh KD, Hasson R, Bolton JP, Lado F, et al. Magnetic field tomography of coherent thalamocortical 40-Hz oscillations in humans. *Proc Natl Acad Sci U S A* 1991;88(24):11037–41.
- [64] Quon RJ, Leslie GA, Camp EJ, Meisenhelter S, Steimel SA, Song Y, et al. 40-Hz auditory stimulation for intracranial interictal activity: A pilot study. *Acta Neurol Scand* 2021;144(2):192–201.
- [65] Lin LC, Lee WT, Wu HC, Tsai CL, Wei RC, Jong YJ, et al. Mozart K.448 and epileptiform discharges: effect of ratio of lower to higher harmonics. *Epilepsy Res* 2010;89(2–3):238–45.
- [66] Buzsáki G, Wang XJ. Mechanisms of gamma oscillations. *Annu Rev Neurosci* 2012;35:203–25.
- [67] Vierling-Claassen D, Siekmeier P, Stufflebeam S, Kopell N. Modeling GABA alterations in schizophrenia: a link between impaired inhibition and altered gamma and beta range auditory entrainment. *J Neurophysiol* 2008;99(5): 2656–71.
- [68] Yizhar O, Fenno LE, Prigge M, Schneider F, Davidson TJ, O'Shea DJ, et al. Neural excitation/inhibition balance in information processing and social dysfunction. *Nature* 2011;477(7363):171–8.
- [69] Zheng Y, Zhang K, Dong L, Tian C. Study on the mechanism of high-frequency stimulation inhibiting low-Mg²⁺-induced epileptiform discharges in juvenile rat hippocampal slices. *Brain Res Bull* 2020;165:1–13.
- [70] Parvizi J, Gururangan K, Razavi B, Chafe C. Detecting silent seizures by their sound. *Epilepsia* 2018;59(4):877–84.
- [71] Maguire MJ. Music and epilepsy: a critical review. *Epilepsia* 2012;53(6):947–61. Jun.
- [72] Perani D, Saccuman MC, Scifo P, Spada D, Andreoli G, Rovelli R, et al. Functional specializations for music processing in the human newborn brain. *Proc Natl Acad Sci U S A* 2010;107(10):4758–63.
- [73] Tervaniemi M, Medvedev SV, Alho K, Pakhomov SV, Roudas MS, Van Zuijen TL, et al. Lateralized automatic auditory processing of phonetic versus musical information: a PET study. *Hum Brain Mapp* 2000;10(2):74–9.
- [74] Garcia-Casares N, Garcia-Arnes JA, Gallego-Bazan Y. Conocimiento actual de la epilepsia musicogena: revision de la literatura cientifica [State of the art in musicogenic epilepsy: a review of the scientific literature]. *Rev Neurol* 2019;69 (7):293–300.
- [75] Pittau F, Tinuper P, Bisulli F, Naldi I, Cortelli P, Bisulli A, et al. Videopolygraphic and functional MRI study of musicogenic epilepsy. A case report and literature review. *Epilepsy Behav* 2008;13:685–92.
- [76] Mehta AD, Ettinger AB, Perrine K, Dhawan V, Patil A, Jain SK, et al. Seizure propagation in a patient with musicogenic epilepsy. *Epilepsy Behav* 2009;14: 421–4.
- [77] Tayah TF, Abou-Khalil B, Gilliam FG, Knowlton RC, Wushensky CA, Gallagher MJ. Musicogenic seizures can arise from multiple temporal lobe foci: intracranial EEG analyses of three patients. *Epilepsia* 2006;47:1402–6.
- [78] Trevathan E, Gewirtz RJ, Cibula JE. Musicogenic seizures of the right superior temporal gyrus origin precipitated by the theme song from “The X Files. *Epilepsia* 1999;40:23.
- [79] Shaw D, Hill D. A case of musicogenic epilepsy. *J Neurol Neurosurg Psychiatry* 1947;10:107–17.
- [80] Stubbe-Teglbjaerg HP. On musicogenic epilepsy. *Acta Psychiatr Neurol* 1949;24: 679–88.
- [81] Dearman HB, Smith BM. A case of musicogenic epilepsy. *JAMA* 1965;193: 1123–5.
- [82] Gloor P. Experiential phenomena of temporal lobe epilepsy. Facts and hypotheses. *Brain* 1990;113:1673–94.
- [83] Rauscher FH, Shaw GL, Ky KN. Music and spatial task performance. *Nature* 1993; 365(6447):611.
- [84] Rauscher FH, Robinson KD, Jens JJ. Improved maze learning through early music exposure in rats. *Neurol Res* 1998;20:427–32.
- [85] Hughes JR, Daaboul Y, Fino JJ, Shaw GL. The “Mozart effect” on epileptiform activity. *Clin Electroencephalogr* 1998;29(3):109–19.
- [86] Hughes JR, Fino JJ, Melyn MA. Is there a chronic change of the “Mozart effect” on epileptiform activity? A case study. *Clin Electroencephalogr* 1999;30:44–5.
- [87] Hughes JR. The Mozart effect. *Epilepsy Behav* 2001;2(5):396–417.
- [88] Hughes JR. The Mozart effect: additional data. *Epilepsy Behav* 2002;3(2):182–4.
- [89] Lin LC, Juan CT, Chang HW, Chiang CT, Wei RC, Lee MW, et al. Mozart K.448 attenuates spontaneous absence seizure and related high-voltage rhythmic spike discharges in Long Evans rats. *Epilepsy Res* 2013;104(3):234–40.
- [90] Xing Y, Qin Y, Jing W, Zhang Y, Wang Y, Guo D, et al. Exposure to Mozart music reduces cognitive impairment in pilocarpine-induced status epilepticus rats. *Cogn Neurodyn* 2016;10(1):23–30.

- [91] Lin LC, Lee MW, Wei RC, Mok HK, Yang RC. Mozart K.448 listening decreased seizure recurrence and epileptiform discharges in children with first unprovoked seizures: a randomized controlled study. *BMC Complement Altern Med* 2014;14:17.
- [92] Rafiee M, Patel K, Groppa DM, Andrade DM, Bercovici E, Bui E, et al. Daily listening to Mozart reduces seizures in individuals with epilepsy: a randomized control study. *Epilepsia Open* 2020;5(2):285–94.
- [93] Grylls E, Kinsky M, Baggott A, Wabnitz C, McLellan A. Study of the Mozart effect in children with epileptic electroencephalograms. *Seizure* 2018;59:77–81.
- [94] Coppola G, Operto FF, Caprio F, Ferraioli G, Pisano S, Viggiano A, et al. Mozart's music in children with drug-refractory epileptic encephalopathies: Comparison of two protocols. *Epilepsy Behav* 2018;78:100–3.
- [95] Bodner M, Turner RP, Schwacke J, Bowers C, Norment C. Reduction of seizure occurrence from exposure to auditory stimulation in individuals with neurological handicaps: a randomized controlled trial. *PLoS One* 2012;7(10): e45303.
- [96] Sesso G, Sicca F. Safe and sound: Meta-analyzing the Mozart effect on epilepsy. *Clin Neurophysiol* 2020;131(7):1610–20.
- [97] Dastgheib SS, Layegh P, Sadeghi R, Foroughipour M, Shoeibi A, Gorji A. The effects of Mozart's music on interictal activity in epileptic patients: systematic review and meta-analysis of the literature. *Curr Neurol Neurosci Rep* 2014;14(1):420.
- [98] Brackney DE, Brooks JL. Complementary and alternative medicine: the Mozart effect on childhood epilepsy—a systematic review. *J Sch Nurs* 2018;34(1):28–37.
- [99] Turner RP. The acute effect of music on interictal epileptiform discharges. *Epilepsy Behav* 2004;5(5):662–8.
- [100] Lin LC, Lee WT, Wang CH, Chen HL, Wu HC, Tsai CL, et al. Mozart K.448 acts as a potential add-on therapy in children with refractory epilepsy. *Epilepsy Behav* 2011;20(3):490–3.
- [101] Lin LC, Lee WT, Wu HC, Tsai CL, Wei RC, Mok HK, et al. The long-term effect of listening to Mozart K.448 decreases epileptiform discharges in children with epilepsy. *Epilepsy Behav* 2011;21(4):420–4.
- [102] Lin LC, Lee MW, Wei RC, Mok HK, Wu HC, Tsai CL, et al. Mozart K.545 mimics Mozart K.448 in reducing epileptiform discharges in epileptic children. *Evid Based Complement Alternat Med* 2012;2012:607517.
- [103] Lin LC, Chiang CT, Lee MW, Mok HK, Yang YH, Wu HC, et al. Parasympathetic activation is involved in reducing epileptiform discharges when listening to Mozart music. *Clin Neurophysiol* 2013;124(8):1528–35.
- [104] D'Alessandro P, Giuglietti M, Baglioni A, Verdolini N, Murgia N, Piccirilli M, et al. Effects of music on seizure frequency in institutionalized subjects with severe/profound intellectual disability and drug-resistant epilepsy. *Psychiatr Danub* 2017;29(Suppl 3):399–404.
- [105] Paprad T, Veeravigrom M, Desudchit T. Effect of Mozart K.448 on interictal epileptiform discharges in children with epilepsy: a randomized controlled pilot study. *Epilepsy Behav* 2021;114(Pt A):107177.
- [106] Quon RJ, Casey MA, Camp EJ, Meisenhelter S, Steimel SA, Song Y, et al. Musical components important for the Mozart K448 effect in epilepsy. *Sci Rep* 2021;11(1): 16490.
- [107] Štillová K, Kiska T, Koriřáková E, Strýček O, Mekyska J, Chrástina J, et al. Mozart effect in epilepsy: why is Mozart better than Haydn? Acoustic qualities-based analysis of stereoelectroencephalography. *Eur J Neurol* 2021;28(5):1463–9.
- [108] Mountcastle VB. The columnar organization of the neocortex. *Brain* 1997;120: 701–22.
- [109] Leng X, Shaw GL, Wright EL. Coding of musical structure and Trion model of cortex. *Music Percept* 1990;8(1):9–62.
- [110] Rafiee M, Istasy M, Valiante TA. Music in epilepsy: Predicting the effects of the unpredictable. *Epilepsy Behav* 2021;122:108164.
- [111] Bak P. How nature works: the science of self-organized criticality. Springer Science & Business Media; 2013.
- [112] Levitin DJ, Chordia P, Menon V. Musical rhythm spectra from Bach to Joplin obey a 1/f power law. *Proc Natl Acad Sci USA* 2012;109:3716–20.
- [113] Miller KJ, Sorensen LB, Ojemann JG, den Nijs M, Sporns O. Power-law scaling in the brain surface electric potential. *PLoS Comput Biol* 2009;5:e1000609.
- [114] Yu Y, Romero R, Lee TS. Preference of sensory neural coding for 1/f signals. *Phys Rev Lett* 2005;18(10):108103. 94.
- [115] Pritchard S. The brain in fractal time: 1/f-like power spectrum scaling of the human electroencephalogram. *Int J Neurosci* 1992;66:119–29.
- [116] Hsu KJ. Fractal geometry of music: From bird songs to Bach. Applications of fractals and chaos. Springer; 1993. p. 21–39.
- [117] Jirsch JD, Urrestarazu E, LeVan P, Olivier A, Dubeau F, Gotman J. High-frequency oscillations during human focal seizures. *Brain* 2006;129(Pt 6):1593–608.
- [118] Teixeira Borges AF, Irmischer M, Brockmeier T, Smit DJA, Mansvelder HD, Linkenkaer-Hansen K. Scaling behaviour in music and cortical dynamics interplay to mediate music listening pleasure. *Sci Rep* 2019;9(1):17700.
- [119] Blood AJ, Zatorre RJ. Intensely pleasurable responses to music correlate with activity in brain regions implicated in reward and emotion. *Proc Natl Acad Sci USA* 2001;98:11818–23.
- [120] Koelsch S, Fritz T, Cramon D, Muller K, Friederici AD. Investigating emotion with music: an fMRI study. *Hum Brain Mapp* 2006;27:239–50.
- [121] Baik JH. Dopamine signaling in reward-related behaviors. *Front Neural Circuits* 2013;7:152.
- [122] Montag C, Reuter M, Axmacher N. How one's favorite song activates the reward circuitry of the brain: personality matters! *Behav Brain Res* 2011;225(2):511–4.
- [123] Fedi M, Berkovic SF, Scheffer IE, O'Keefe G, Marini C, Mulligan R, et al. Reduced striatal D1 receptor binding in autosomal dominant nocturnal frontal lobe epilepsy. *Neurology* 2008;71(11):795–8.
- [124] Landvogt C, Buchholz HG, Bernedo V, Schreckenberger M, Werhahn KJ. Alteration of dopamine D2/D3 receptor binding in patients with juvenile myoclonic epilepsy. *Epilepsia* 2010;51(9):1699–706.
- [125] Werhahn KJ, Landvogt C, Klimpe S, Buchholz HG, Yakushev I, Siessmeier T, et al. Decreased dopamine D2/D3-receptor binding in temporal lobe epilepsy: an [18F] fallypride PET study. *Epilepsia* 2006;47(8):1392–6.
- [126] Deransart C, Riban V, Lê B, Marescaux C, Depaulis A. Dopamine in the striatum modulates seizures in a genetic model of absence epilepsy in the rat. *Neuroscience* 2000;100(2):335–44.
- [127] Kaneyuki H, Yokoo H, Tsuda A, Yoshida M, Mizuki Y, Yamada M, et al. Psychological stress increases dopamine turnover selectively in mesoprefrontal dopamine neurons of rats: reversal by diazepam. *Brain Res* 1991;557(1–2): 154–61.
- [128] Lotufo PA, Valiengo L, Benseñor IM, Brunoni AR. A systematic review and meta-analysis of heart rate variability in epilepsy and antiepileptic drugs. *Epilepsia* 2012;53(2):272–82.
- [129] Lin LC, Chiang CT, Lee MW, Mok HK, Yang YH, Wu HC, et al. Parasympathetic activation is involved in reducing epileptiform discharges when listening to Mozart music. *Clin Neurophysiol* 2013;124(8):1528–35.
- [130] Min BK, Bystritsky A, Jung KI, Fischer K, Zhang Y, Maeng LS, et al. Focused ultrasound-mediated suppression of chemically-induced acute epileptic EEG activity. *BMC Neurosci* 2011;12:23.
- [131] Hakimova H, Kim S, Chu K, Lee SK, Jeong B, Jeon D. Ultrasound stimulation inhibits recurrent seizures and improves behavioral outcome in an experimental model of mesial temporal lobe epilepsy. *Epilepsy Behav* 2015;49:26–32.
- [132] Chen SG, Tsai CH, Lin CJ, Lee CC, Yu HY, Hsieh TH, et al. Transcranial focused ultrasound pulsation suppresses pentylenetetrazol induced epilepsy in vivo. *Brain Stimul* 2020;13(1):35–46.
- [133] Li X, Yang H, Yan J, Wang X, Yuan Y, Li X. Seizure control by low-intensity ultrasound in mice with temporal lobe epilepsy. *Epilepsy Res* 2019;154:1–7.
- [134] Zhang M, Li B, Lv X, Liu S, Liu Y, Tang R, et al. Low-intensity focused ultrasound-mediated attenuation of acute seizure activity based on EEG brain functional connectivity. *Brain Sci* 2021;11(6):711.
- [135] Yamaguchi T, Hori T, Hori H, Takasaki M, Abe K, Taira T, et al. Magnetic resonance-guided focused ultrasound ablation of hypothalamic hamartoma as a disconnection surgery: a case report. *Acta Neurochir (Wien)* 2020;162(10): 2513–7.
- [136] Abe K, Yamaguchi T, Hori H, Sumi M, Horisawa S, Taira T, et al. Magnetic resonance-guided focused ultrasound for mesial temporal lobe epilepsy: a case report. *BMC Neurol* 2020;20(1):160.
- [137] Brinker ST, Preiswerk F, White PJ, Mariano TY, McDannold NJ, Bubrick EJ. Focused ultrasound platform for investigating therapeutic neuromodulation across the human hippocampus. *Ultrasound Med Biol* 2020;46(5):1270–4.
- [138] Parker WE, Weidman EK, Chazen JL, Niogi SN, Uribe-Cardenas R, Kaplitt MG, et al. Magnetic resonance-guided focused ultrasound for ablation of mesial temporal epilepsy circuits: modeling and theoretical feasibility of a novel noninvasive approach. *J Neurosurg* 2019;14:1–8.
- [139] Lee CC, Chou CC, Hsiao FJ, Chen YH, Lin CF, Chen CJ, et al. Pilot study of focused ultrasound for drug-resistant epilepsy. *Epilepsia* 2022;63(1):162–75.
- [140] Stern JM, Spivak NM, Becerra SA, Kuhn TP, Korb AS, Kronemyer D, et al. Safety of focused ultrasound neuromodulation in humans with temporal lobe epilepsy. *Brain Stimul* 2021;14(4):1022–31.
- [141] Prieto ML, Ömer O, Khuri-Yakub BT, Maduke MC. Dynamic response of model lipid membranes to ultrasonic radiation force. *PLoS One* 2013;8(10):e77115.
- [142] Tyler WJ, Tufail Y, Finsterwald M, Tauchmann ML, Olson EJ, Majestic C. Remote excitation of neuronal circuits using low-intensity, low-frequency ultrasound. *PLoS One* 2008;3(10):e3511.
- [143] Bekar L, Libionka W, Tian GF, Xu Q, Torres A, Wang X, et al. Adenosine is crucial for deep brain stimulation-mediated attenuation of tremor. *Nat Med* 2008;14: 75–80.
- [144] Zou J, Yi S, Niu L, Zhou H, Lin Z, Wang Y, et al. Neuroprotective effect of ultrasound neuromodulation on kainic acid-induced epilepsy in mice. *IEEE Trans Ultrason Ferroelectr Freq Control* 2021;68(9):3006–16.
- [145] Graham F. COP26: Glasgow Climate Pact signed into history. *Nature* 2021.